Public health policy and dioxin in the environment

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Presented at the Symposium on

Dioxin: Exposures, health effects

and public health policy

September 7, 2005
Centre for Public Health Research
Wellington campus, Massey University

Dioxin terminology

- There are a large number of dioxins and dioxin-like compounds including the furans and PCBs.
- These compounds can be grouped together with weightings based on their toxicological properties.

Toxicity Equivalency Factors (TEFs) for Halogenated Hydrocarbons (ATSDR, 1998)

CDFs		CDDs		PCBs	
monoCDFs	0	monoCDDs	0	3,3'4,4'-tetraCB	0.0005
diCDFs	0	diCDDs	0	3,3',4,4'5-pentaCB	0.1
triCDFs	0	triCDDs	0	2,3,3',4,4'-pentaCB	0.0001
2,3,7,8-tetraCDF	0.1	2,3,7,8-TCDD	1	2,3,4,4',5-pentaCB	0.0005
other tetraCDFs	0	other tetraCDDs	0	2,3',4,4',5-pentaCB	0.0001
1,2,3,7,8-pentaCDF	0.05	2,3,7,8-pentaCDD	0.5	2',3,4,4',5-pentaCB	0.0001
2,3,4,7,8-pentaCDF	0.5	other pentaCDDs	0	3,3',4,4',5,5'-hexaCB	0.01
other pentaCDFs	0			2,3,3',4,4',5-hexaCB	0.0005
2,3,7,8-hexaCDF	0.1	2,3,7,8-hexaCDD	0.1	2,3,3',4,4',5'-hexaCB	0.0005
other hexaCDFs	0	other hexaCDDs	0	2,3',4,4',5,5'-hexaCB	0.00001
2,3,7,8-heptaCDF	0.01	2,3,7,8-heptaCDD	0.01	2,3,3',4,4',5,5'-heptaCB	0.0001
otherheptaCDFs	0	other heptaCDDss	0	2,2',3,3',4,4',5-heptaCB	0.0001
octaCDF	0.001	octaCDD	0.001	2,2',3,4,4',5,5'-heptaCB	0.00001

Dioxin terminology

- For brevity, I will be using “dioxin” to mean the famous dioxin: 2,3,7,8-TCDD
- And “dioxin equivalents” to mean the combined exposure to dioxin-like compounds expressed as equivalents of 2,3,7,8-TCDD

EXPOSURE TO DIOXINS

- Found almost everywhere in the environment
- People are exposed through the diet with meats, dairy products and fish being the main sources
- Levels have been decreasing over the last decade
- Agent Orange contained 2,4-D and 2,4,5-T. The 2,4,5-T was contaminated with dioxin

Epidemiology

- Is the study of the causes of health and disease in human populations
- It is multidisciplinary in nature
- Epidemiology has known scientific limitations, but is essential to obtain human evidence of disease causation

The first question for this presentation

Does dioxin cause human cancer?

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

- 1. Consider chance as the explanation of findings
- 2. Consider bias as the explanation of findings
- 3. Examine consistency
- 4. Assess strength of the association
- 5. Examine dose-response findings
- 6. Assess temporal relationships
- 7. Examine biological plausibility

WANTING "STRENGTH OF ASSOCIATION" MEANS WE SHOULD FOCUS ON HIGH DOSE POPULATIONS

- If we focus on high dose populations, findings are less likely to be due to chance
- Findings are also less likely due to bias
- We are more likely to identify dose-response relationships in studies including high doses

For these reasons, causal inference for chemical exposure disease causation should give priority to high dose studies

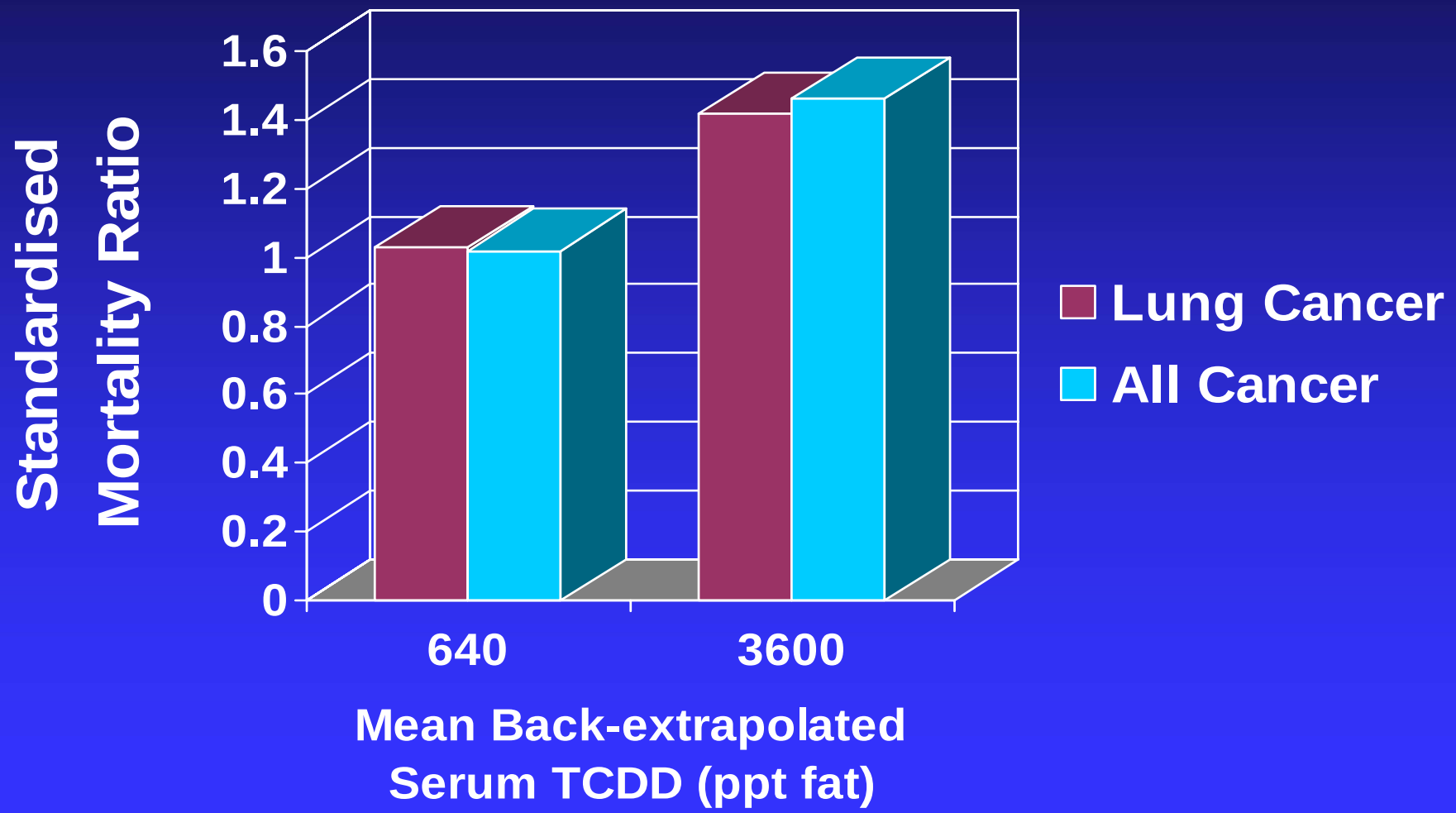
High dose exposure to dioxin can be documented

- Roughly half the dioxin (2,3,7,8-TCDD) human intake on any one day will still be in the body ten years later
- This means that, for dioxin, we do not have to rely on past exposure approximations often necessary in epidemiological studies
- For causal inference, we can focus on studies with documented high dose exposure, and ignore studies where biological measures indicate no evidence of significant dioxin exposure.

Fingerhut *et al*, 1991. The NIOSH cohort study

- 5172 male workers in 12 plants across U.S. that produced chemicals contaminated with TCDD
- Follow-up from 1942 through 1987
- Serum dioxin concentrations were measured on some of the exposed workers
- smoking data were available for some workers

Lung and All Cancer Mortality (Fingerhut *et al*, 1991)



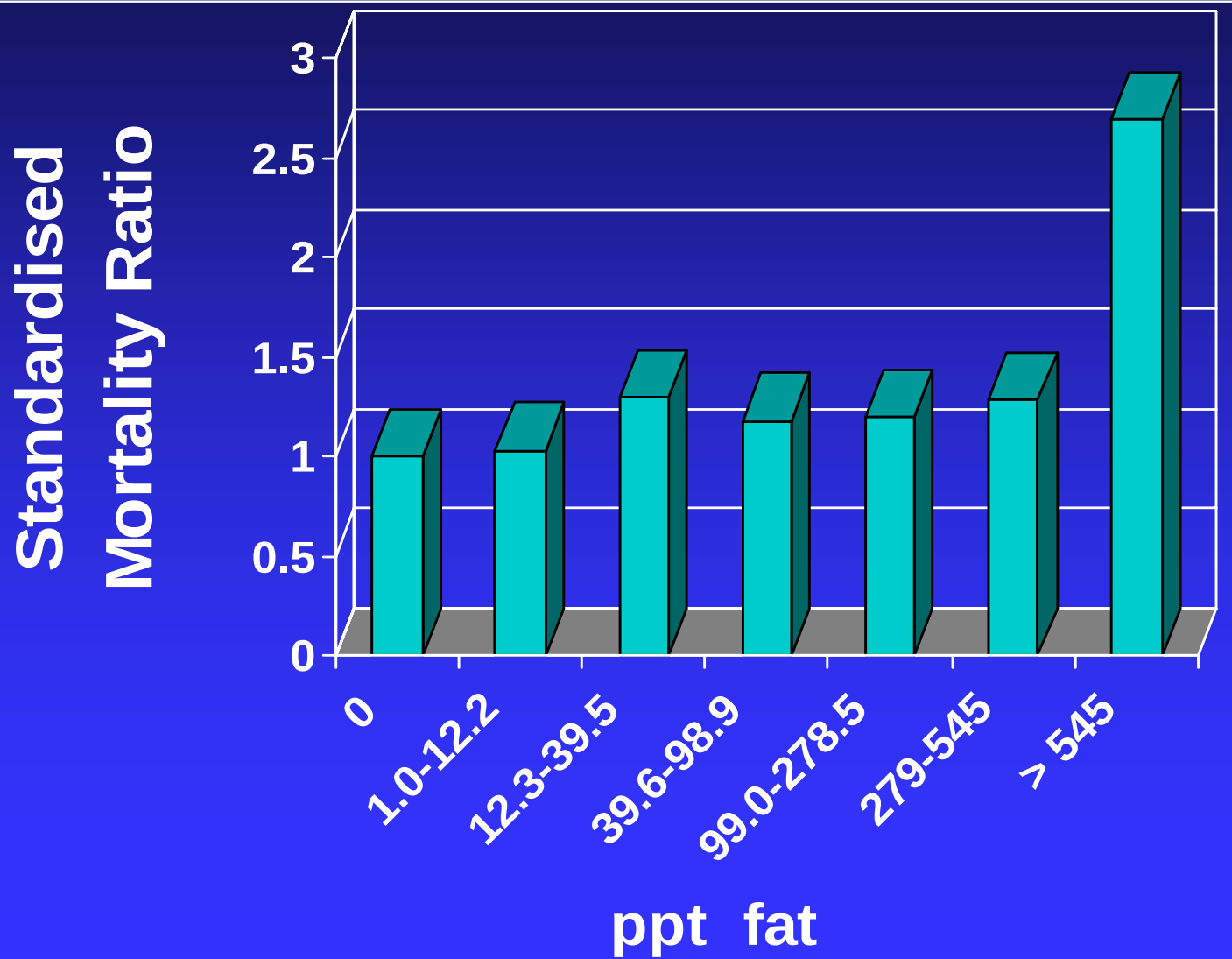
These findings are astonishing

- There was an overall increase in cancer mortality
- No one or two cancer sites predominated, as has usually been found for major human carcinogens (e.g. smoking, asbestos, benzidine, vinyl chloride, benzene, arsenic)
- In fact the major contributor to increased cancer mortality (lung cancer) had the same relative risk estimate (1.4) as the all cancer relative risk (1.4)

Flesch-Janys, 1995, 1998

- 1189 male workers in a German pesticide manufacturing plant
- Follow-up from 1952 through 1992
- PCDD/F serum or adipose tissue levels obtained from 236 members of cohort

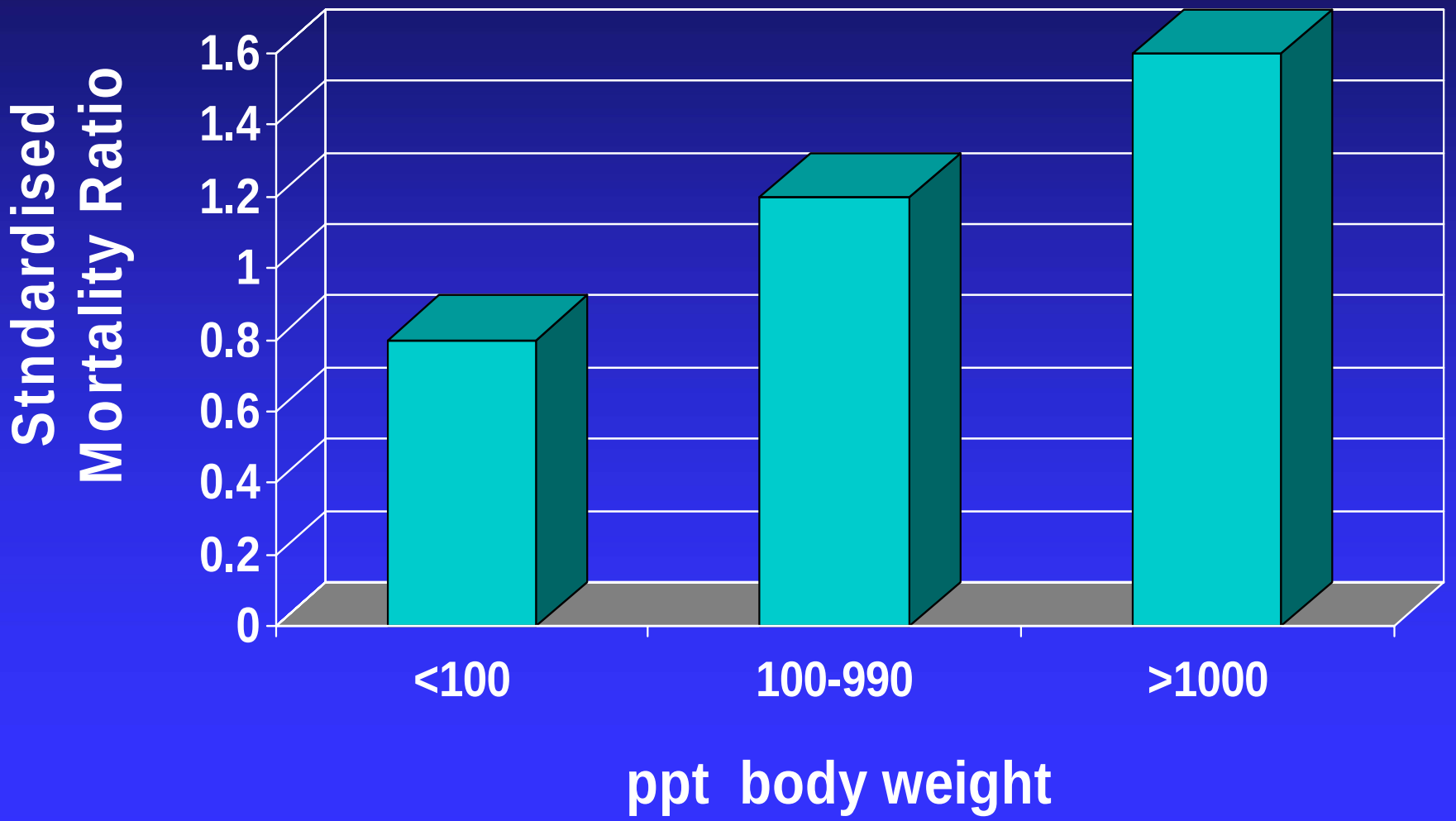
SMRs for All Cancer Mortality by TCDD Levels (Flesch-Janys, 1995)



Ott and Zober, 1996

- Consists of 243 male workers involved in 1953 reactor accident at BASF TCP plant in Germany
- All members of cohort were affected by chloracne
- Serum levels of 2,3,7,8-TCDD available for 138 members

SMRs for All Cancer Mortality by TCDD Dose Group (Ott and Zober, 1996)



Cancer mortality in industrial cohort studies with high exposure levels (IARC, 1997)

	ALL CANCERS			LUNG CANCER		
	Obs.	SMR	95% CI	Obs.	SMR	95% CI
Fingerhut, 1991	114	1.5	1.2-1.8	40	1.4	1.0-1.9
Becher, 1996	105	1.3	1.0-1.5	33	1.4	1.0-2.0
Hooiveld, 1996	51	1.5	1.1-1.9	14	1.0	0.5-1.7
Ott and Zober, 1996	18	1.9	1.1-3.0	7	2.4	1.0-5.0
Combined	**286**	**1.4**	**1.2-1.6**	**94**	**1.4**	**1.1-1.7**

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$p < 0.001$ $p < 0.01$

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

- 1. Consider chance as the explanation of findings

- increased lung cancer mortality **p <0.01**
- increased all cancer mortality **p<0.001**

These findings are not likely to be due to chance

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

- 1.
- 2. Consider bias as the explanation of findings
- 3.
- 4.
- 5.
- 6.
- 7.

Bias?

- There is no basis for expecting bias to increase cancer mortality for all four studies
- Smoking must be considered, but there is sufficient evidence within these studies to dismiss it as an explanation for the increased cancer risks

Adjustment for smoking in the NIOSH cohort

- Lifetime smoking histories available for 223 workers
- They smoked a little more than the general US population
- In the high exposure group with more than 20 years latency:
  - unadjusted lung cancer SMR **1.42**
  - smoking adjusted lung cancer SMR **1.37**
- In addition, chronic obstructive pulmonary disease mortality was not increased, which would be expected if they smoked more

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

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STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

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- 4. Assess strength of the association
- 5.
- 6.
- 7.

Strength of association

- The lung cancer SMRs about 1.4 on their own are not strong
- However all cancer SMRs around 1.4 are rarely found.
- For occupational cancer, only heavily exposed asbestos cohorts result in all cancer SMRs of 1.4 and more.
  - **Note: There may have been some exposure to asbestos in these cohorts … but they were not "heavily exposed" asbestos cohorts.**

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

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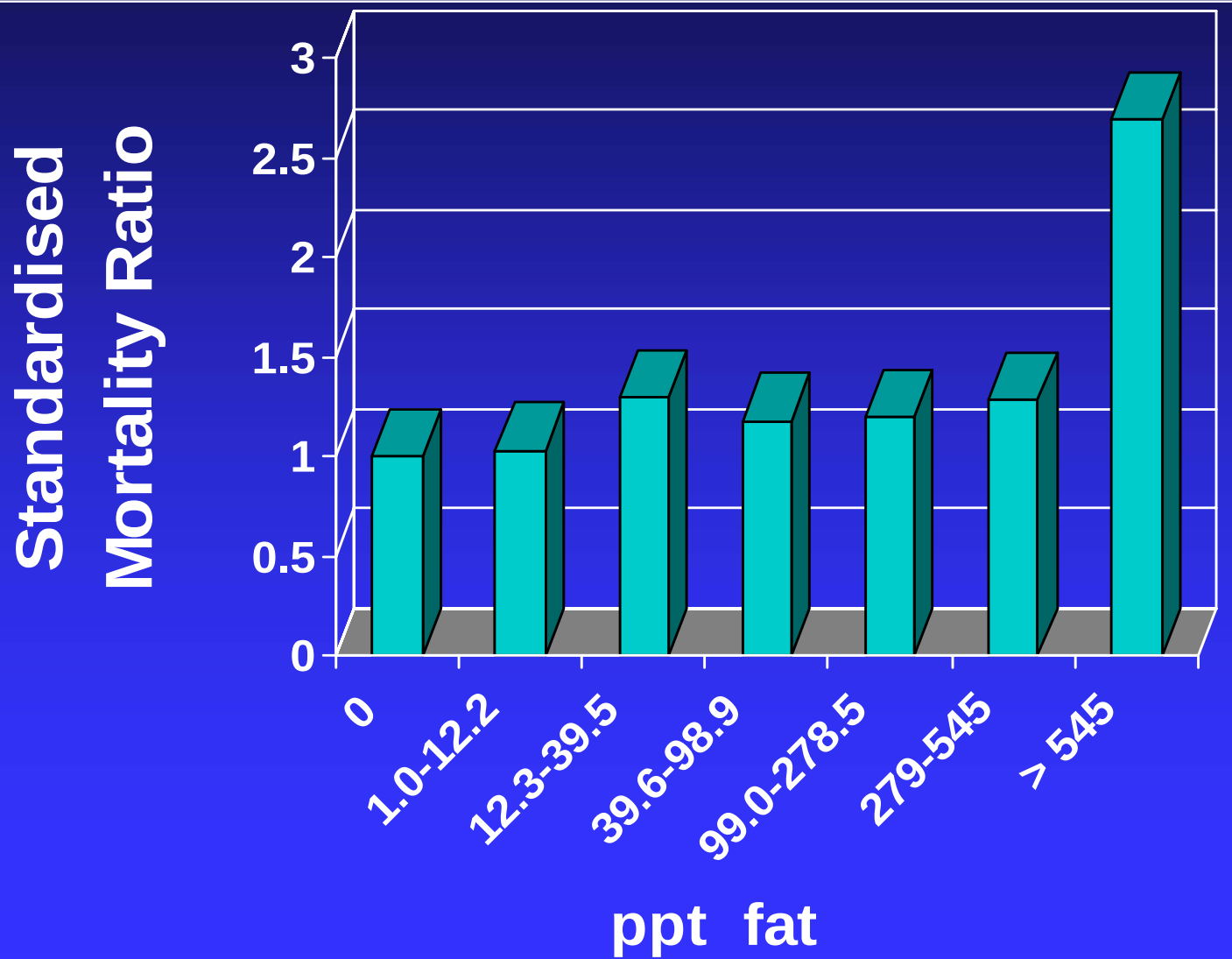
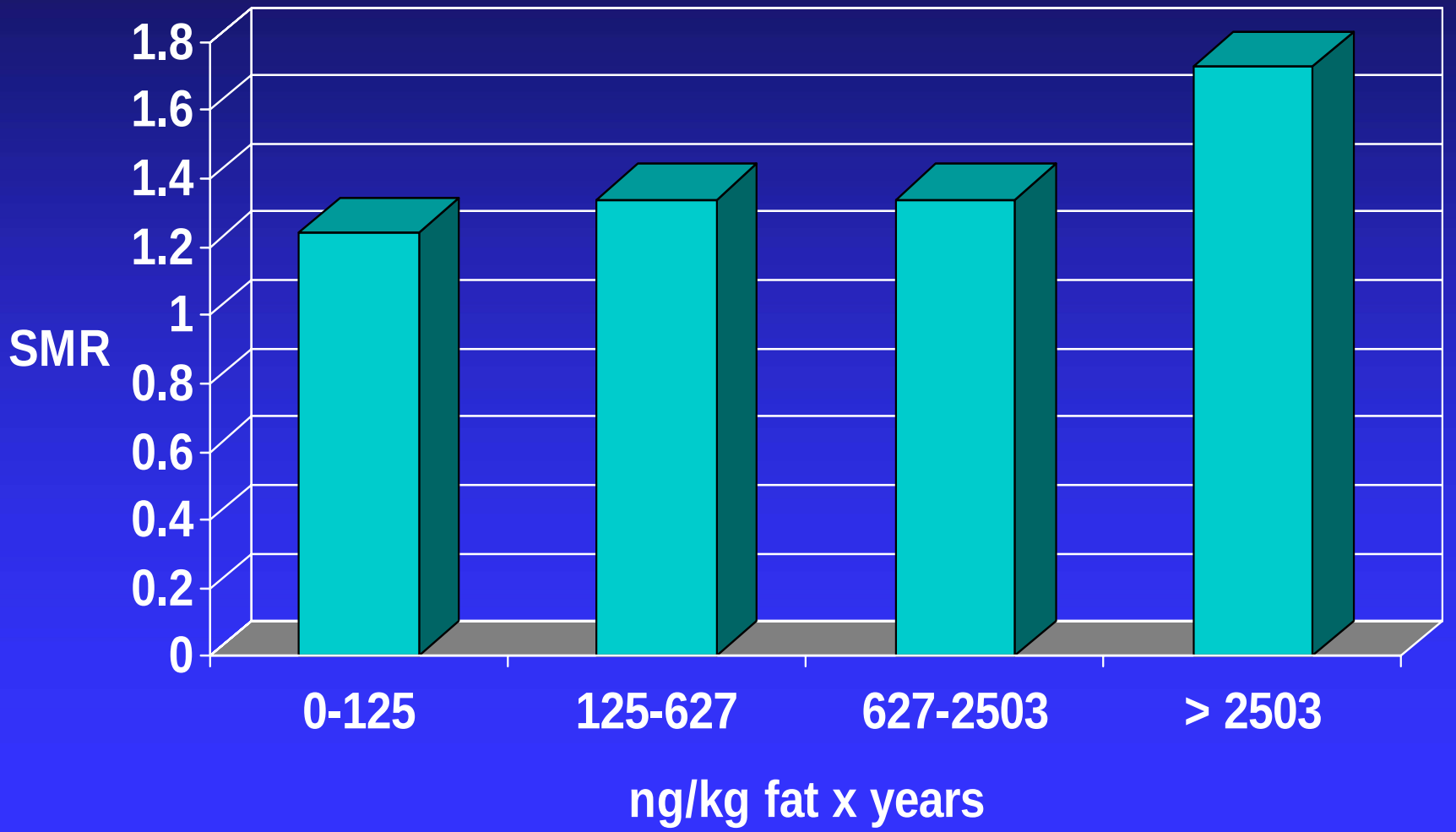
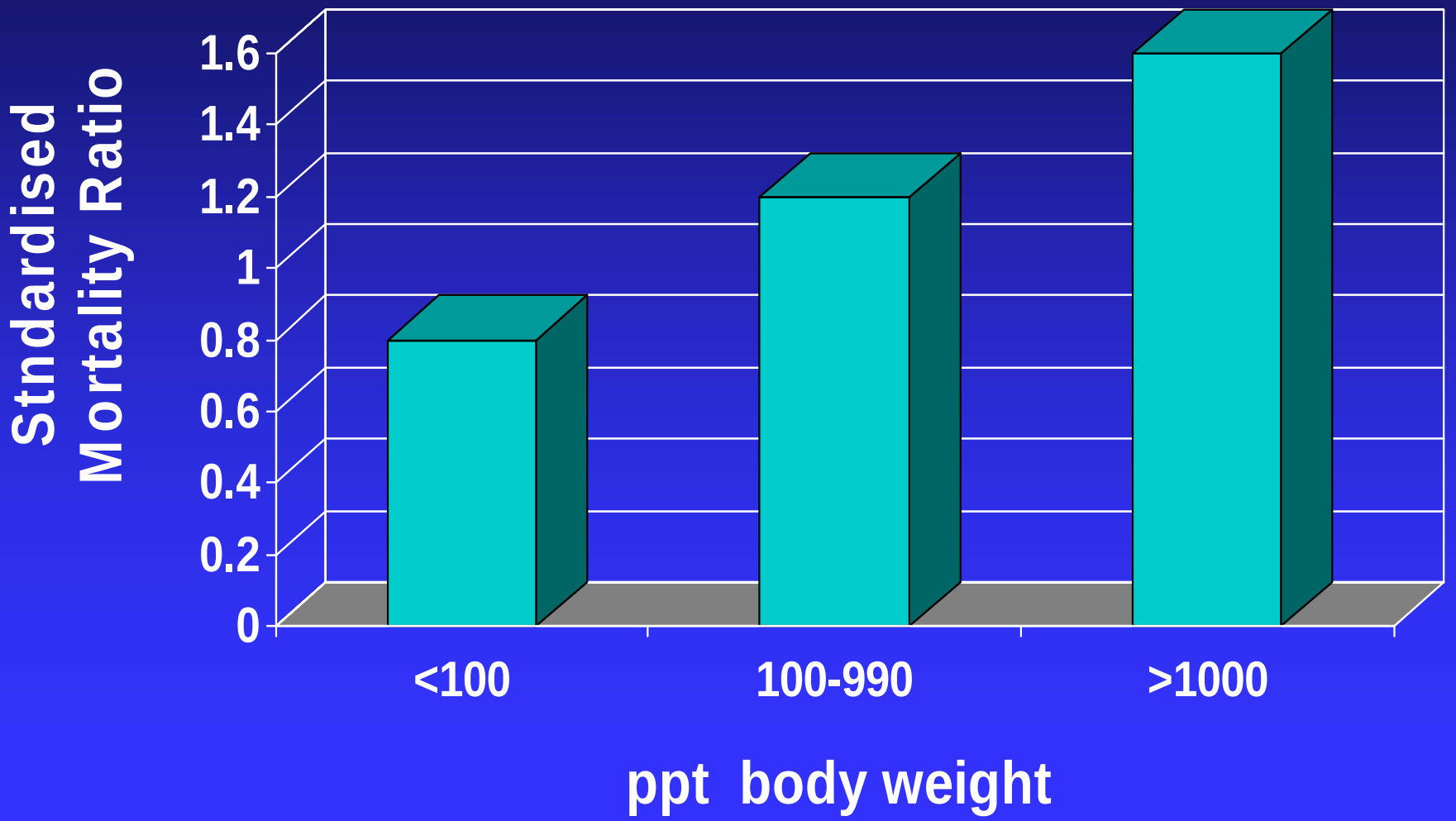
SMRs for All Cancer Mortality by TCDD Levels (Flesch-Janys, 1995)



SMRs for All Cancer Mortality by Serum TCDD Exposure Above Background Levels (Flesch-Janys *et al*, 1998)



SMRs for All Cancer Mortality by TCDD Dose Group (Ott and Zober, 1996)



STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

- 1.
- 2.
- 3.
- 4.
- 5.
- 6. Assess temporal relationships
- 7.

Temporal relationship between exposure and outcome

- Each of the studies had significant periods of follow-up more than 20 years from first exposure
- The increased risks were identified with appropriate latency.

STEPS FOR CAUSAL INFERENCE IN EPIDEMIOLOGY

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- 7. Examine biological plausibility

THE ANIMAL EVIDENCE USED BY THE IARC WORKING GROUP

- 2,3,7,8-TCDD administered at low doses by different routes causes tumors at multiple sites in rats and mice.
- 2,3,7,8-TCDD has also been shown to cause cancer in hamsters. This species is considered the most resistant to its acute toxic effects.

THE MECHANISTIC EVIDENCE USED BY THE IARC WORKING GROUP

- 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown through several lines of evidence to act through a mechanism involving the Ah receptor
- This receptor is highly conserved in an evolutionary sense and functions the same in humans as in experimental animals
- Tissue concentrations of 2,3,7,8-TCDD are similar in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays

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BASIS FOR IARC WORKING GROUP EVALUATION

- **Human evidence: There is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-TCDD**
- **Animal evidence: There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-TCDD**
- **Mechanistic evidence: There is *strong evidence* in exposed humans that 2,3,7,8-TCDD acts through a relevant mechanisms of carcinogenicity**

Difficulties with the human evidence

- There was no single cancer site that stood out with consistent evidence and strong associations
- We are accustomed to making carcinogen determination on specific cancer sties
- For these reasons, the epidemiological evidence on its own was assessed as “limited”

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

Volume 69
Polychlorinated Dibenzo-*para*-Dioxins and Polychlorinated Dibenzofurans
1997

Overall Evaluation:
2,3,7,8-TCDD is carcinogenic to humans
Group 1

ESTABLISHED NON-CANCER EFFECTS OF 2,3,7,8-TCDD IN HUMANS

- Chloracne and other dermal effects
- Alterations in liver enzymes and its ability to metabolize
- Slight increases in risk of diabetes and abnormal glucose tolerance

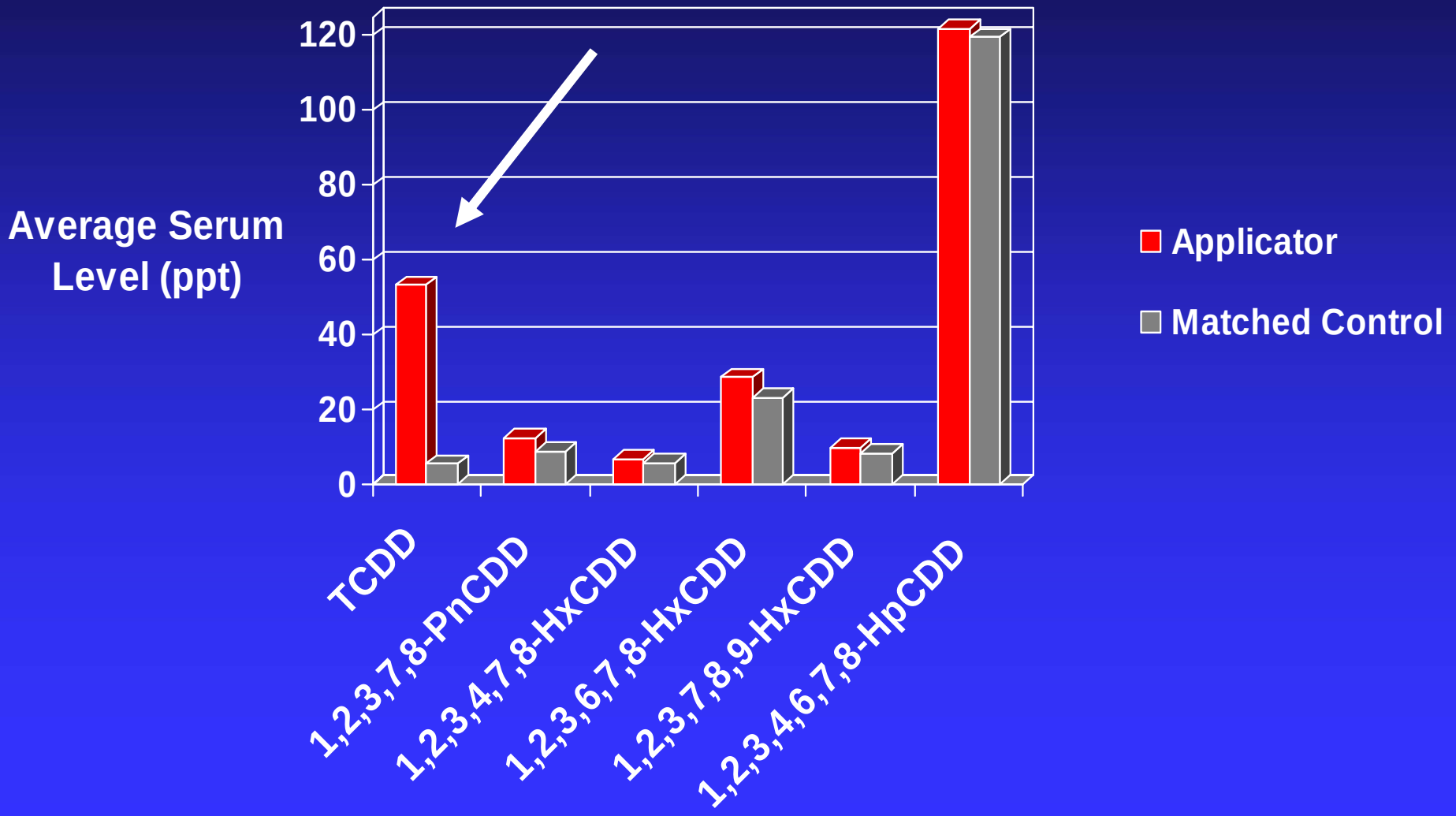
All Cause, All Cancer and Noncancer Mortality from Three Occupational Cohort Studies

	Observed	Expected	SMR
Flesch-Janys, 1998			
All Cause	413	357.7	1.2
All Cancer	124	88.1	1.4
Noncancer	289	269.6	1.1
Ott and Zober, 1996			
All Cause	92	102.2	0.9
All Cancer	31	25.8	1.2
Noncancer	61	76.4	0.8
Fingerhut, 1991			
All Cause	1052	1062.6	1.0
All Cancer	265	230.4	1.2
Noncancer	787	832.2	1.0

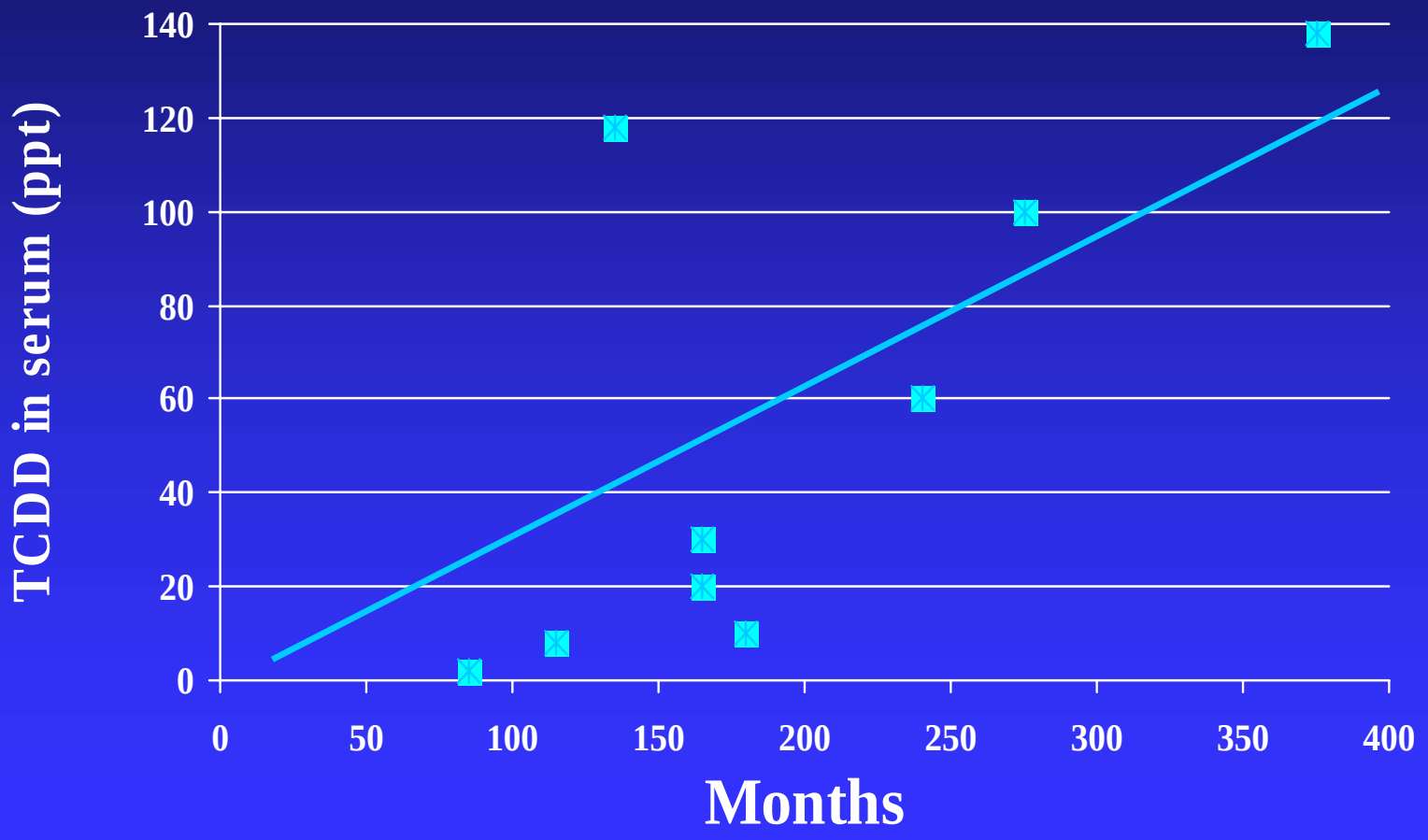
Non-cancer mortality

- Dioxin might increase mortality from other causes than cancer.
- However, if so, their overall mortality impact would be much less than mortality from cancer
- It is reassuring that the very high exposure occupational cohorts did not experience overall increases in non-cancer mortality.

Average Serum Levels (lipid-adjusted) of PCDDs in Nine 2,4,5-T Applicators and Nine Matched Control Subjects (Smith *et al.*, 1992)



Concentration of TCDD in serum of applicators in relation to total months spent spraying 2,4,5-T. Level of TCDD is adjusted for total level of lipids in serum. (Smith et al., 1992)



Male sprayers (2,4,5-T, 2,4-D) family data

(Smith *et al.*, 1981)

	Sprayers	Agricultural Contractors
Average age at time of survey	39.0	38.0
Average age at marriage	22.7	22.6
Average age when first child born	23.7	23.7
Average number of children at time of survey	2.6	2.7

Pregnancy Outcomes in the Years 1969-1980 for 3 Exposure Groups (Smith *et al.*, 1982)

Pregnancy Outcome	Group 1 Not Exposed	Group 2 Sprayed Chemicals But Not 2,4,5-T	Group 3 Sprayed 2,4,5-T	Relative Risks Group 3 vs. Group 1	90% C.I.
Normal birth	352	100	427	...	...
Congenital defect	9	4	13	1.19	0.58-2.45
Miscarriage	40	9	43	0.89	0.61-1.30
Stillbirth	0	0	3	...	...

Reproductive effects

- Epidemiological evidence of reproductive effects of dioxin is inconclusive
- The major concern raised by animal studies involves maternal exposure

NONCANCER EFFECTS OF 2,3,7,8-TCDD IN ANIMALS

- Short and long-term exposure can result in effects on almost every organ system
- Most sensitive effects are immune, reproductive and developmental
- Although there are large species differences in the doses that produce lethality, most species respond to the toxic effects of TCDD at similar doses

Derivation of WHO Tolerable Daily Intake of 1-4 pg TEQ/kg bw (Rolaf van Leeuwen, 1999)

	Maternal Body Burden Over Background (ng/kg bw)	Related Human EDI (pg/kg bw/day)	Reference
RATS:			
Decrease sperm count in offspring	28	14	Gray, 1997
Immune suppression in offspring	50	25	Gehrs, 1997; 1998
Increased congenital malformations in offspring	73	37	Gray, 1997
MONKEYS:			
Neurobehavioral (object learning) effects in offspring	42	21	Schantz, 1989
Endometriosis	42	21	Rier, 1993

Population dioxin surveillance

- Widespread population exposure, although at low levels, warrants consideration of population surveillance programs

- One example is the population surveillance program in New Zealand involving serum and breast milk samples.

New Zealand serum surveillance

- Involves a cross-sectional random sample of the population
- serum samples are pooled according to specified stratification criteria.

Summary results (TEQ, ppt), by region of the c ountry

	Region			
	Auckland/ Northland	Waikato/ Bay of Plenty	Lower North Island	South Island
Dioxins	14.5	15.3	11.8	12.8
PCBs	7.9	7.5	6.5	6.7

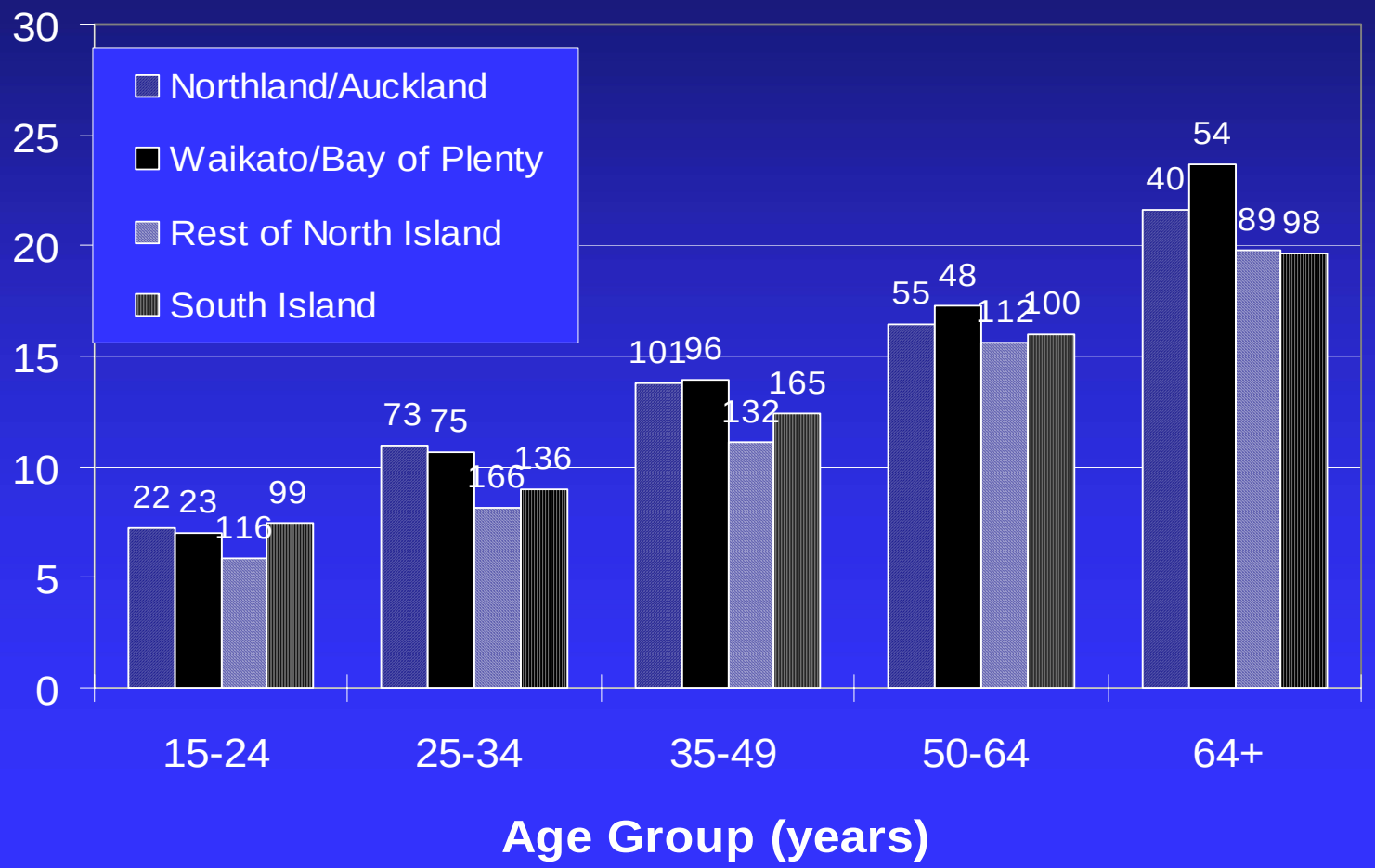
Summary results (TEQ, ppt), by ethnicity and sex, for dioxins and PCBs

	Male		Female	
	Maori	Non-Maori	Maori	Non-Maori
Dioxins	8.6	9.4	9.5	9.1
PCBs	6.1	6.0	5.7	5.8

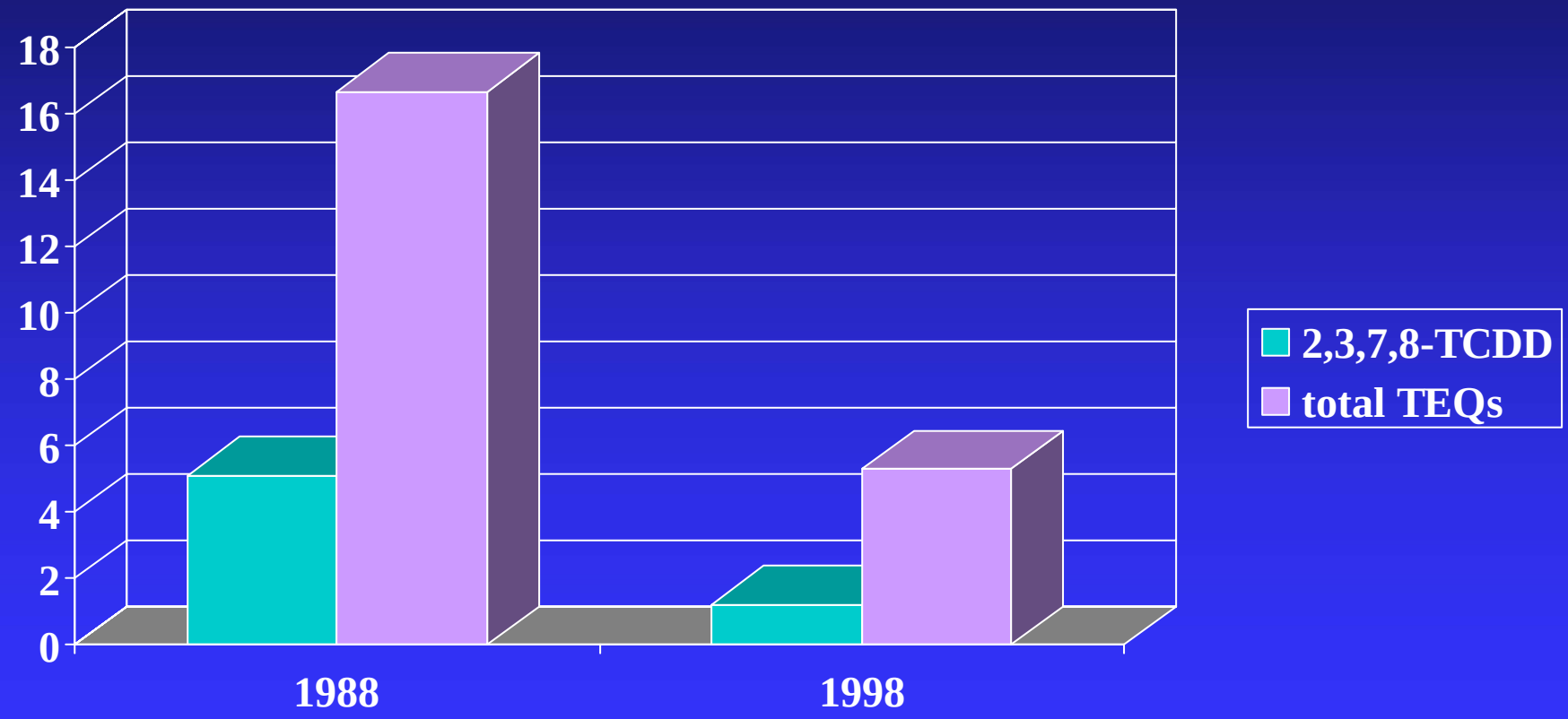
Summary results (TEQ, ppt), by age-group for dioxins and PCBs

	Age-group (years)				
	15-24	25-34	35-49	50-64	65+
Dioxins	6.7	9.3	12.6	16.1	20.7
PCBs	5.9	5.8	6.5	7.6	9.2

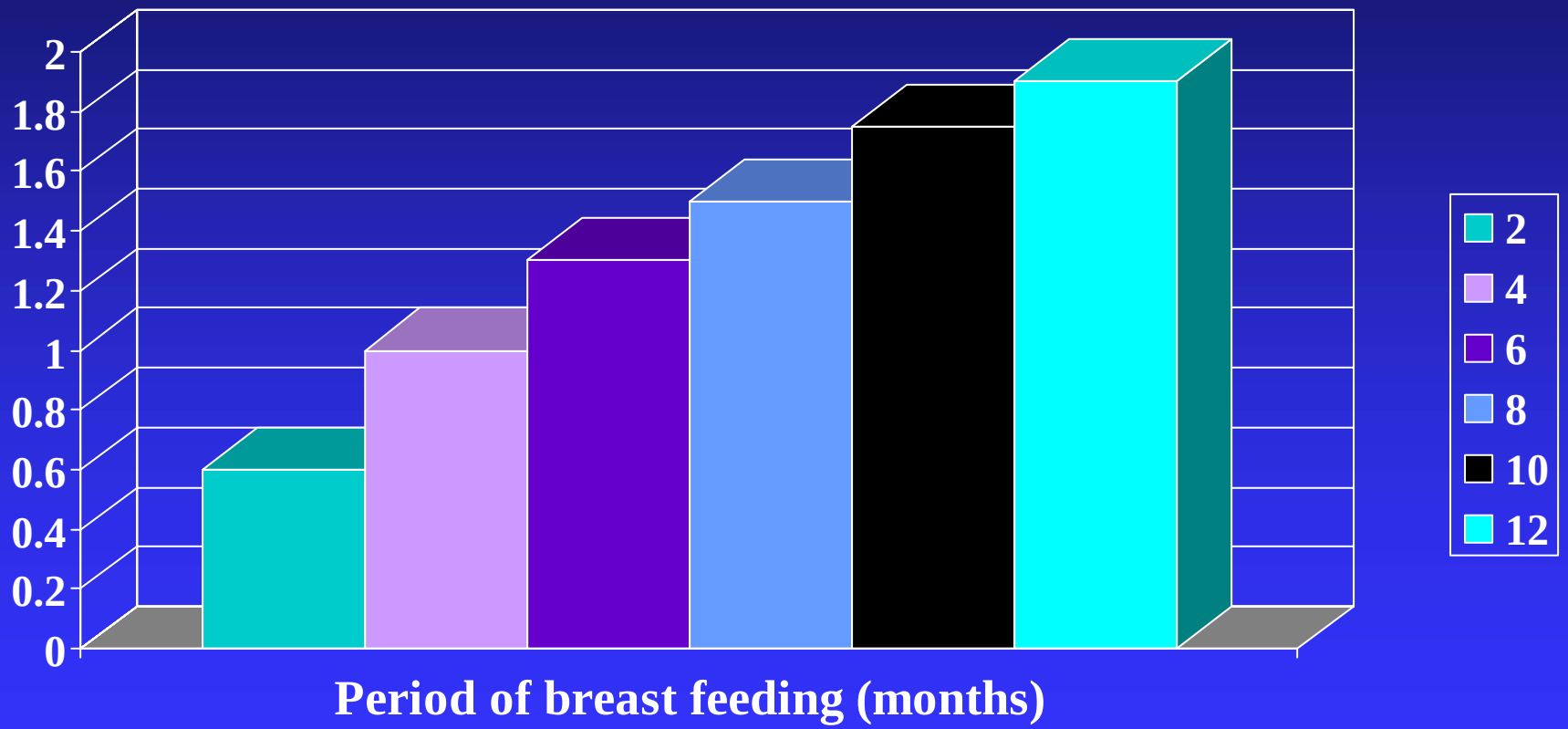
Total dioxin TEQs (ppt) in serum, by geographic area, across age-groups



New Zealand breast milk concentrations in 1988 and 1998 in pg/g fat



Ratio of concentration of 2,3,7,8-TCDD in infant compared to mother by duration of breast feeding



Some recommendations in the NZ HRA, 2001

- A precautionary approach should be adopted.
- A goal of on-going reduction in population body burdens should be stated.
- Population burdens should be monitored, perhaps every 5-10 years.

A health risk appraisal for the New Zealand population, Ministry for the Environment, 2001, www.mfe.govt.nz/issues/wastes/organochlorines/HRA.pdf

Serum TCDD Levels for the General Population and Three Occupational Cohorts Back-extrapolated to the End of their Exposure

- TCDD concentration for general population is ~5 ppt
- Midpoint of highest exposure group from Flesch-Janys *et al.*
- Mean for group with >/ 20 years latency and >/ 1 yr exposure from Fingerhut *et al.*,
- Highest exposure group from Ott and Zober, 1996

LOW-DOSE EXTRAPOLATION

- Assumes any level of exposure may carry some level of risk (no threshold)
- Involves extrapolation by mathematical modeling of the dose-response curve to estimate the risk at likely human intakes (low doses)
- Is considered health conservative
- Actual shape of the dose-response curve is likely to remain unknown
- Low-dose risk estimates vary widely depending on the model used

The problem with dioxin incremental risk assessment ignoring background

Consider a point source such as an incinerator.

If you project the maximum ground level concentration of dioxin emissions producing a 1 in a million risk estimate:

1. **Background air concentrations without the incinerator are about 20-40 times higher than that already.**

2. **The person living there already has in their body a dioxin concentration associated with about a 1 in 1000 cancer risk estimate**

Incremental risk assessments of dioxin are absurd and result in massive waste of public health resources

Smith AH, Sciortino S, Goeden H, Wright CC.

Consideration of Background Exposures in the Management of Hazardous Waste Sites: A New Approach to Risk Assessment.

Risk Analysis, 16:619-625, 1996

PUBLIC HEALTH RISK ASSESSMENT

- First assess background population exposure
- Chemicals would then be classified based on potential health risks associated with background exposures
- Cleanup decisions could be based on both potential health risks and potential contribution of a waste site or point source to an already existing population exposure
- Advantage is that resources would be allocated to reduce the most important sources of human exposure

Just tell me I’m safe

- **Scientist**: Give me a big grant and I will tell you what’s really happening (in about ten years).
- **Regulator**: Just give me one simple number.
- **Risk assessor**: Why do you want just one number when for 10% more cost I can give you 20 numbers?
- **Real person**: To ****…!! with all your numbers. Just tell me I’m safe.

Cost-benefit analysis

How should we value the “benefits” of having “safe” air food and water?

- **By costing avoided disease in the future?**
- **Or by valuation of the immediate gain from confidence we live in a healthy environment?**
- **Or both?**

Costing cancers

- Assume a cancer death is prevented that would otherwise occur 30 years from now
- Assume at that time you cost it to be $100,000 (???) preventing it would be a gain of $100,000
- If you invested $13,136 today at 7% you would have your million dollars in 30 years. So in today's money you only gain $13,136. (i.e you should only spend $13,136 to prevent a cancer 30 years from now).

Discounting future health benefits ignores current values

- The current value of $100,000 projected 150 years (6 generations) is **$4**
- With this approach, we can ignore concerns about future generations. You should not spend any money much now to protect them.
- Forget about global warming.
- Yet we do “value” the protection of the environment for future generations

Some recommendations in the NZ HRA, 2001

- A precautionary approach should be adopted.
- A goal of on-going reduction in population body burdens should be stated.
- Population burdens should be monitored, perhaps every 5-10 years.

A health risk appraisal for the New Zealand population, Ministry for the Environment, 2001

Of course

- more research
- including epidemiological studies
- are needed

Point source exposures

2,4,5-T manufacture, New Plymouth

Timber treatment with PCP

A Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Exposures in Paritutu, New Zealand

- “Having established dioxin exposure in this community, a logical next step is to establish the feasibility of an epidemiological study using geospatial analysis to determine whether or not the exposed Paritutu community demonstrates evidence of health effects as have been observed previously in other exposed communities.”

Comparison of dioxin concentrations

Combined U.S. cohorts	3600
BASF cohort Germany	1000-2400
Chlorophenol plant Germany	345-3890
Chlorophenol plants, Netherlands	1842
Seveso, Zones A and B	136
Paritutu, New Plymouth	6.5
General population	1

Comparison of approximate population numbers

Combined U.S. cohorts	5000
BASF cohort Germany	243
Chlorophenol plant Germany	
Chlorophenol plants, Netherlands	
Seveso, Zones A and B	6800
Paritutu, New Plymouth	50
General population	-

A Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Exposures in Paritutu, New Zealand

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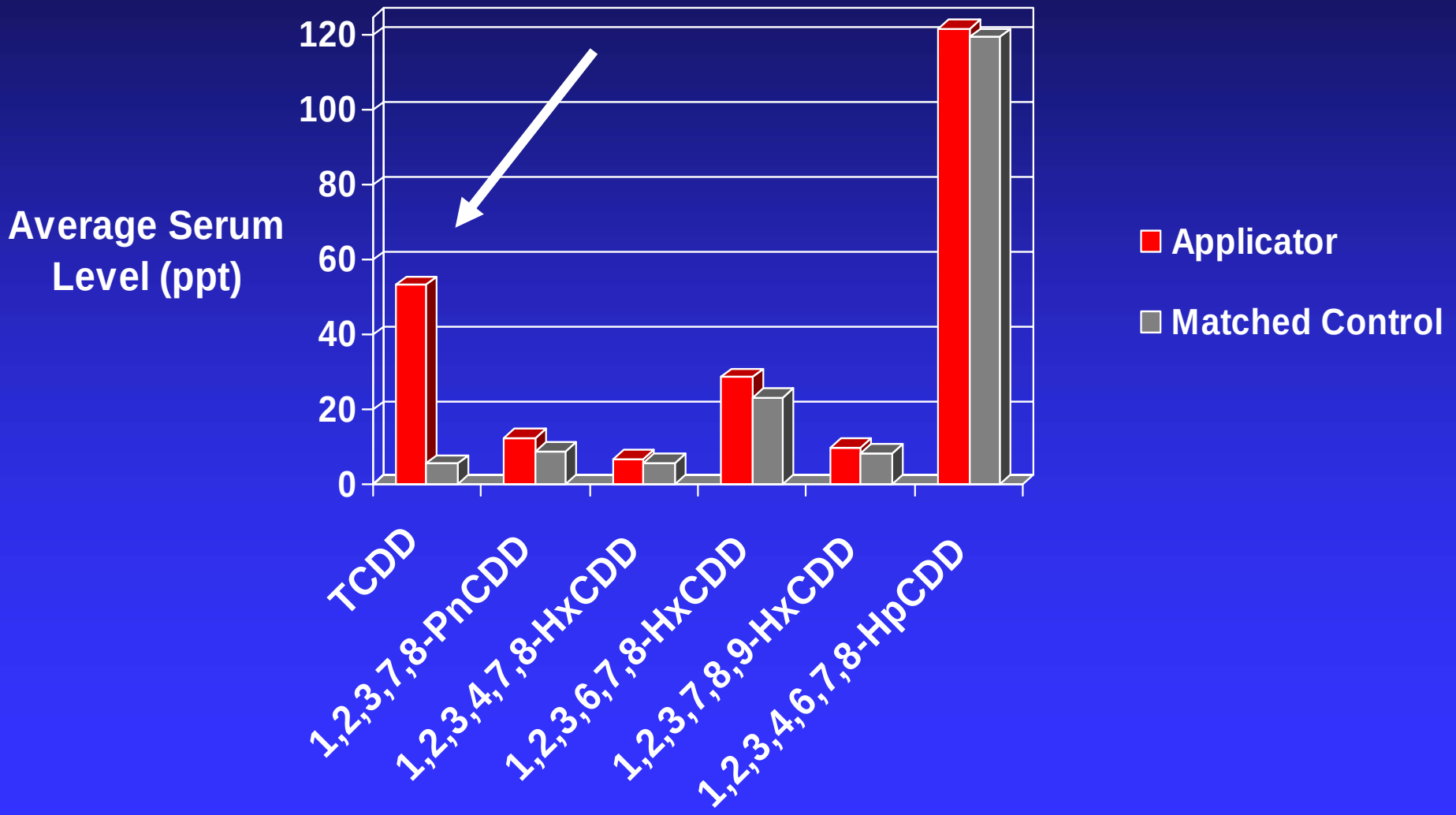
- People with these levels of exposure should be reassured that although their dioxin concentrations are above average, they are way below levels which have been shown to cause health effects.

Need to further study the cohort of workers

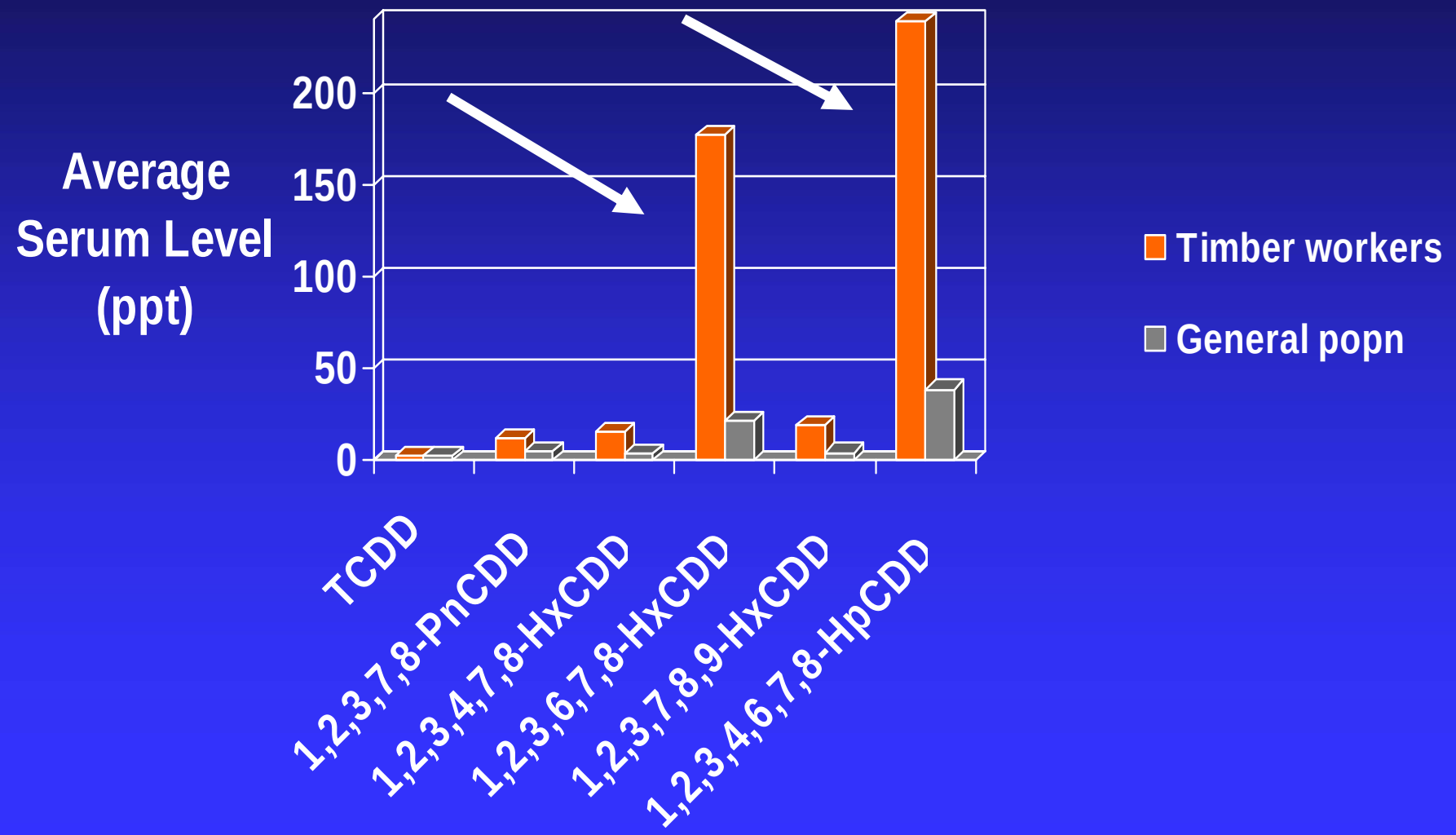
- in contrast to those living nearby, there are good reasons to study the workers in the plant who would have experienced much higher exposure to dioxin

- the Health Research Council of New Zealand is to be commended for funding the important study being conducted by Massey University led by Professor Neil Pearce.

Average Serum Levels (lipid-adjusted) of PCDDs in Nine 2,4,5-T Applicators and Nine Matched Control Subjects (Smith *et al.*, 1992)



Average Serum Levels (lipid-adjusted) of PCDDs in four timber workers exposed to PCP compared to general population



Some recommendations in the NZ HRA, 2001

- A precautionary approach should be adopted.
- A goal of on-going reduction in population body burdens should be stated.
- Population burdens should be monitored, perhaps every 5-10 years.
- Assessment of special populations with point source exposure

Evaluation of toxicity of dioxins and dioxin-like PCBs: A health risk appraisal for the New Zealand population

http://www.mfe.govt.nz/publications/hazardous/dioxin-evlauation-feb01.pdf